angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.
Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. Gallbladder disease

Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.

4. Liver tumors

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in two studies, in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are rare.

5. Cancer of the reproductive organs and breasts

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer.
Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table. [See table above.]
In the above table, the risk of death from any birth control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.
The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of low-dose oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth related
** Deaths are method related

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor or clinic immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or clinic to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark colored urine, or light colored bowel movements (indicating possible liver problems)

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. Vaginal bleeding

Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your doctor or clinic.

2. Contact lenses

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or clinic.

3. Fluid retention

Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or clinic.

4. Melasma

A spotty darkening of the skin is possible, particularly of the face, which may persist.

5. Other side effects

Other side effects may include nausea and vomiting, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.
If any of these side effects bother you, call your doctor or clinic.

GENERAL PRECAUTIONS

1. Missed periods and use of oral contraceptives before or during early pregnancy

There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your doctor or clinic before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, you may be pregnant. If you missed two consecutive menstrual periods, you may be pregnant. Check with your doctor or clinic immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.
There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects, when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these findings have not been seen in more recent studies. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor or clinic. You should check with your doctor or clinic about risks to your unborn child of any medication taken during pregnancy.

2. While breast feeding

If you are breast feeding, consult your doctor or clinic before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, oral contraceptives may decrease the amount and quality of your milk. If possible, do not use oral contraceptives while breast feeding. You should use another method of contraception since breast feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast feed for longer periods of time. You should consider starting oral contraceptives only after you have weaned your child completely.

3. Laboratory tests

If you are scheduled for any laboratory tests, tell your doctor or clinic you are taking birth control pills. Certain blood tests may be affected by birth control pills.

4. Drug interactions

Certain drugs may interact with birth control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital), anticonvulsants such as carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand), and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST TRANSMISSION OF HIV (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES SUCH AS CHLAMYDIA, GENITAL HERPES, GENITAL WARTS, GONORRHEA, HEPATITIS B, AND SYPHILIS.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:
   Before you start taking your pills.
   Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
   If you miss pills you could get pregnant. This includes starting the pack late.
   The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS.
   If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills. On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
   Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS:

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL. It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:
   The 21-pill pack has 21 "active" [white] pills (with hormones) to take for 3 weeks, followed by 1 week without pills.
   The 28-pill pack has 21 "active" [white] pills (with hormones) to take for 3 weeks, followed by 1 week of reminder [green] pills (without hormones).
3. ALSO FIND:
   1) where on the pack to start taking the pills,
   2) in what order to take the pills (follow the arrows) and
   3) the week numbers printed on the pack.
4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up in case you miss pills.
   AN EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS:

You have a choice of which day to start taking your first pack of pills. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START:

1. Pick the day label strip that starts with the first day of your period (this is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins.)

Continued on next page

Organon—Cont.

2. Place this day label strip in the cycle tablet dispenser over the area that has the days of the week (starting with Sunday) imprinted in the plastic.
Note: If the first day of your period is a Sunday, you can skip steps #1 and #2.
3. Take the first "active" [white] pill of the first pack during the first 24 hours of your period.
4. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:

1. Take the first "active" [white] pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam or the sponge are good back-up methods of birth control.

WHAT TO DO DURING THE MONTH:

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.
2. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:**
21 pills: Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.
28 pills: Start the next pack on the day after your last "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS:

If you **MISS 1** [white] "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** [white] "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 2** [white] "active" pills in a row in **THE 3RD WEEK:**
1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills.
You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 3** OR MORE [white] "active" pills in a row (during the first 3 weeks).
1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills.
You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:

If you forget any of the 7 [green] "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE [WHITE] "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately one percent (i.e., one pregnancy per 100 women per year) if taken every day as directed, but more typical failure rates are about 3%. If failure does occur, the risk to the fetus is minimal.

PREGNANCY AFTER STOPPING THE PILL

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.
There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE

Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your doctor, clinic or pharmacist.

OTHER INFORMATION

Your doctor or clinic will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and your doctor or clinic believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your doctor or clinic if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your doctor or clinic because this is a time to determine if there are early signs of side effects of oral contraceptive use.
Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES

In addition to preventing pregnancy, use of combination oral contraceptives may provide certain benefits. They are:

- menstrual cycles may become more regular
- blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- pain or other symptoms during menstruation may be encountered less frequently.
- ectopic (tubal) pregnancy may occur less frequently.
- noncancerous cysts or lumps in the breast may occur less frequently.
- acute pelvic inflammatory disease may occur less frequently.
- oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth control pills, ask your doctor, clinic or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read. The Professional Labeling is also published in a book entitled *Physicians' Desk Reference*, available in many book stores and public libraries.

 5310190 Revised 12/94

Shown in Product Identification Guide, page 325

DURABOLIN® Ⓒ Ⓡ
(nandrolone phenpropionate injection, USP)

HOW SUPPLIED

25 mg/mL—5 mL vials.
50 mg/mL—2 mL vials.

HUMEGON™ Ⓡ
(menotropins for injection, USP)
FOR INTRAMUSCULAR INJECTION

DESCRIPTION

Humegon™ (menotropins for injection, USP) is a purified preparation of gonadotropins. Menotropins are extracted from the urine of postmenopausal females and possess follicle-stimulating hormone (FSH) and luteinizing hormone (LH) activity. The ratio of FSH bioactivity and LH bioactivity in menotropins is adjusted to approximate unity by the addition of human chorionic gonadotropin purified from the urine of pregnant women. Each vial of Humegon™ contains 75 IU or 150 IU of follicle-stimulating hormone activity and 75 IU or 150 IU of luteinizing hormone activity, respectively, plus 10.5 mg lactose, hydrous NF; 0.25 mg monosodium phosphate, monohydrate USP; 0.25 mg disodium phosphate, anhydrous USP; sodium hydroxide NF or phosphoric acid NF to adjust pH; in a sterile, lyophilized form.
Humegon™ is administered by intramuscular injection.
Humegon™ is biologically standardized for FSH and LH gonadotropin activities and the potencies are based on the results of *in vivo* bioassays, which are in agreement with the recommendations of the World Health Organization Expert Committee on Biological Standardization (1982).
Both FSH and LH as well as hCG are glycoproteins that are acidic and water soluble.
Therapeutic class: Infertility.

CLINICAL PHARMACOLOGY

The geometric mean absolute bioavailability of FSH from the 150 IU intramuscular (IM) dose compared to the 150 IU intravenous (IV) dose was 76%. Following single dose IM injections of 75, 150, and 300 IU Humegon™ to healthy male volunteers, FSH dose response was less than proportional between the 75 and 150 IU doses and between the 150 and 300 IU doses. The mean FSH elimination half-lives of 75, 150, and 300 IU IM were 37 hrs, 30 hrs, and 36 hrs, respectively, and 31 hrs following 150 IU IV administration.
Repeated daily IM administration of 150 IU Humegon™ to seven women on 8 consecutive days led to a gradual accumulation of FSH levels which plateaued in 3–4 days. It took 4–5 days for the elevated FSH levels to return to pretreatment levels. These findings underline the importance of very careful and frequent monitoring of the patient in order to reduce the danger of ovarian hyperstimulation.
Women:
Humegon™ administered for seven to twelve days produces ovarian follicular growth in women who do not have primary ovarian failure. Treatment with Humegon™ in most instances results only in follicular growth and maturation. In order to induce ovulation, human chorionic gonadotropin (hCG) must be given following the administration of Humegon™ when clinical assessment of the patient indicates that sufficient follicular maturation has occurred.
Men:
Humegon™ administered concomitantly with human chorionic gonadotropin (hCG) for at least three months induces spermatogenesis in men with primary or secondary pituitary hypofunction who have achieved adequate masculinization with prior hCG therapy.

INDICATIONS AND USAGE

Women:
Humegon™ and hCG given in a sequential manner are indicated for the induction of ovulation and pregnancy in the anovulatory infertile patient, in whom the cause of anovulation is functional and is not due to primary ovarian failure.
Humegon™ and hCG may also be used to stimulate the development of multiple follicles in ovulatory patients participating in an *in vitro* fertilization program.
Men:
Humegon™ with concomitant hCG is indicated for the stimulation of spermatogenesis in men who have primary or secondary hypogonadotropic hypogonadism, and idiopathic infertility.
Humegon™ with concomitant hCG has proven effective in inducing spermatogenesis in men with primary hypogonadotropic hypogonadism due to a congenital factor or prepubertal hypophysectomy and in men with secondary hypogonadotropic hypogonadism due to hypophysectomy, craniopharyngioma, cerebral aneurysm, or chromophobe adenoma.

SELECTION OF PATIENTS

Women:
1. Before treatment with Humegon™ is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. Except for those patients enrolled in an *in vitro* fertilization program, this should include a hysterosalpingogram (to rule out uterine and tubal pathology) and documentation of anovulation by means of basal body temperature, serial vaginal smears, examination of cervical mucus, determination of serum (or urinary) progesterone, urinary pregnanediol, and endometrial biopsy. Patients with tubal pathology should receive Humegon™ only if enrolled in an *in vitro* fertilization program.
2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.
3. Careful examination should be made to rule out the presence of an early pregnancy.
4. Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of anovulatory disorders. Cervical dilation and curettage should always be done for diagnosis before starting Humegon™ therapy in such patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities.

ADVERSE REACTIONS

During clinical studies with the MONISTAT 3 Vaginal Suppository (miconazole nitrate, 200 mg) 301 patients were treated. The incidence of vulvovaginal burning, itching or irritation was 2%. Complaints of cramping (2%) and headaches (1.3%) were also reported. Other complaints (hives, skin rash) occurred with less than a 0.5% incidence. The therapy-related dropout rate was 0.3%.

OVERDOSE

Overdose of miconazole nitrate in humans has not been reported to date. In mice, rats, guinea pigs and dogs, the oral LD 50 values were found to be 578.1, >640, 275.9 and >160 mg/kg, respectively.

DOSAGE AND ADMINISTRATION

MONISTAT 3 Vaginal Suppositories: One suppository (miconazole nitrate, 200 mg) is inserted intravaginally once daily at bedtime for three consecutive days. Before prescribing another course of therapy, the diagnosis should be reconfirmed by smears and/or cultures to rule out other pathogens.

HOW SUPPLIED

MONISTAT 3 Suppositories (miconazole nitrate, 200 mg) are available as 2.5 gm, elliptically shaped white to off-white suppositories in packages of three (NDC 0062-5437-01) with a vaginal applicator. Store at 59–86°F (15–30°C).

7 DAY CREAM THERAPY
MONISTAT-DERM®
(miconazole nitrate 2%)
Cream
For Topical Use Only

DESCRIPTION

MONISTAT-DERM (miconazole nitrate 2%) Cream contains miconazole nitrate* 2%, formulated into a water-miscible base consisting of pegoxol 7 stearate, peglicol 5 oleate, mineral oil, benzoic acid, butylated hydroxyanisole and purified water.

ACTIONS

Miconazole nitrate is a synthetic antifungal agent which inhibits the growth of the common dermatophytes, *Trichophyton rubrum, Trichophyton mentagrophytes,* and *Epidermophyton floccosum,* the yeast-like fungus, *Candida albicans,* and the organism responsible for tinea versicolor *(Malassezia furfur).*

INDICATIONS

For topical application in the treatment of tinea pedis (athlete's foot), tinea cruris, and tinea corporis caused by *Trichophyton rubrum, trichophyton mentagrophytes,* and *Epidermophyton floccosum,* in the treatment of cutaneous candidiasis (moniliasis), and in the treatment of tinea versicolor.

CONTRAINDICATIONS

MONISTAT-DERM (miconazole nitrate 2%) Cream has no known contraindications.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued. For external use only. Avoid introduction of MONISTAT-DERM Cream into the eyes.

ADVERSE REACTIONS

There have been isolated reports of irritation, burning, maceration, and allergic contact dermatitis associated with the application of MONISTAT-DERM.

DOSAGE AND ADMINISTRATION

Sufficient MONISTAT-DERM Cream should be applied to cover affected areas twice daily (morning and evening) in patients with tinea pedis, tinea cruris, tinea corporis, and cutaneous candidiasis, and once daily in patients with tinea versicolor. If MONISTAT-DERM Cream is used in intertriginous areas, it should be applied sparingly and smoothed in well to avoid maceration effects.

Early relief of symptoms (2 to 3 days) is experienced by the majority of patients and clinical improvement may be seen fairly soon after treatment is begun; however, *Candida* infections and tinea cruris and corporis should be treated for two weeks and tinea pedis for one month in order to reduce the possibility of recurrence. If a patient shows no clinical improvement after a month of treatment, the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatment.

HOW SUPPLIED

MONISTAT-DERM (miconazole nitrate 2%) Cream containing miconazole nitrate at 2% strength is supplied in 15 g. (NDC 0062-5434-02), 1 oz. (NDC 0062-5434-01) and 3 oz. (NDC 0062-5434-03) tubes.

*Chemical name: 1-[2,4-dichloro-β-[(2,4- dichlorobenzyl) oxy]phenethyl] imidazole mononitrate.

Revised January 1992 643-10-357-6
Shown in Product Identification Guide, page 326

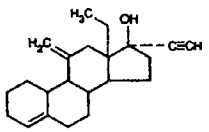
ORTHO-CEPT®
(desogestrel and ethinyl estradiol) Tablets

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

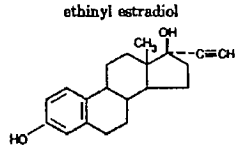
DESCRIPTION

ORTHO-CEPT 21 and ORTHO-CEPT 28 Tablets provide an oral contraceptive regimen of 21 orange round tablets each containing 0.15 mg desogestrel (13-ethyl-11-methylene-18,19-dinor-17 alpha-pregn-4-en-20-yn-17-ol) and 0.03 mg ethinyl estradiol (19-nor-17 alpha-pregna-1,3,5 (10)-trien-20-yne-3,17,diol). Inactive ingredients include vitamin E, corn starch, povidone, stearic acid, colloidal silicon dioxide, lactose, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, talc and ferric oxide. ORTHO-CEPT 28 also contains 7 green tablets containing the following inactive ingredients: lactose, pregelatinized starch, magnesium stearate, FD&C Blue No. 1 Aluminum Lake, ferric oxide, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and talc.

desogestrel



ethinyl estradiol



CLINICAL PHARMACOLOGY

Pharmacodynamics

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus, which increase the difficulty of sperm entry into the uterus, and changes in the endometrium which reduce the likelihood of implantation.

Receptor binding studies, as well as studies in animals and humans, have shown that 3-keto-desogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with minimal intrinsic androgenicity[91,92]. Desogestrel, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in SHBG, resulting in lower serum levels of free testosterone[96–99].

Pharmacokinetics

Desogestrel is rapidly and almost completely absorbed and converted into 3-keto-desogestrel, its biologically active metabolite. Following oral administration, the relative bioavailability of desogestrel, as measured by serum levels of 3-keto-desogestrel, is approximately 84%.

In the third cycle of use after a single dose of ORTHO-CEPT, maximum concentrations of 3-keto-desogestrel of 2,805±1,203 pg/mL (mean±SD) are reached at 1.4±0.8 hours. The area under the curve ($AUC_{0-\infty}$) is 33,858±11,043 pg/mL·hr after a single dose. At steady state, attained from at least day 19 onwards, maximum concentrations of 5,840±1,667 pg/mL are reached at 1.4±0.9 hours. The minimum plasma levels of 3-keto-desogestrel at steady state are 1,400±560 pg/mL. The AUC_{0-24} at steady state is 52,299±17,878 pg/mL·hr. The mean $AUC_{0-\infty}$ for 3-keto-desogestrel at single dose is significantly lower than the mean AUC_{0-24} at steady state. This indicates that the kinetics of 3-keto-desogestrel are non-linear due to an increase in binding of 3-keto-desogestrel to sex hormone-binding globulin in the cycle, attributed to increased sex hormone-binding globulin levels which are induced by the daily administration of ethinyl estradiol. Sex hormone-binding globulin levels increased significantly in the third treatment cycle from day 1 (150±64 nmol/L) to day 21 (230±59 nmol/L).

The elimination half-life for 3-keto-desogestrel is approximately 38±20 hours at steady state. In addition to 3-keto-desogestrel, other phase I metabolites are 3α-OH-desogestrel, 3β-OH-desogestrel, and 3α-OH-5α-H-desogestrel. These other metabolites are not known to have any pharmacologic effects, and are further converted in part by conjugation (phase II metabolism) into polar metabolites, mainly sulfates and glucuronides.

Ethinyl estradiol is rapidly and almost completely absorbed. In the third cycle of use after a single dose of ORTHO-CEPT, the relative bioavailability is approximately 83%.

In the third cycle of use after a single dose of ORTHO-CEPT, maximum concentrations of ethinyl estradiol of 95±34 pg/mL are reached at 1.5±0.8 hours. The $AUC_{0-\infty}$ is 1,471±268 pg/mL·hr after a single dose. At steady state, attained from at least day 19 onwards, maximum ethinyl estradiol concentrations of 141±48 pg/mL are reached at about 1.4±0.7 hours. The minimum serum levels of ethinyl estradiol at steady state are 24±8.3 pg/mL. The AUC_{0-24}, at steady state is 1,117±302 pg/mL·hr. The mean $AUC_{0-\infty}$ for ethinyl estradiol following a single dose during treatment cycle 3 does not significantly differ from the mean AUC_{0-24} at steady state. This finding indicates linear kinetics for ethinyl estradiol.

The elimination half-life is 26±6.8 hours at steady state. Ethinyl estradiol is subject to a significant degree of presystemic conjugation (phase II metabolism). Ethinyl estradiol escaping gut wall conjugation undergoes phase I metabolism and hepatic conjugation (phase II metabolism). Major phase I metabolites are 2-OH-ethinyl estradiol and 2-methoxy-ethinyl estradiol. Sulfate and glucuronide conjugates of both ethinyl estradiol and phase I metabolites, which are excreted in bile, can undergo enterohepatic circulation.

INDICATIONS AND USAGE

ORTHO-CEPT Tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Oral contraceptives are highly effective. Table I lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of these methods can result in lower failure rates.

[See table at bottom of next page.]

In a clinical trial with ORTHO-CEPT, 1,195 subjects completed 11,656 cycles and a total of 10 pregnancies were reported. This represents an overall user-efficacy (typical user-efficacy) pregnancy rate of 1.12 per 100 women-years. This rate includes patients who did not take the drug correctly.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebral vascular or coronary artery disease
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with formulations of higher doses of estrogens and progestogens than those in common use today. The effect of long term use of the oral contraceptives with formulations of lower doses of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a *ratio* of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Co-

Continued on next page

Ortho—Cont.

hort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (Adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six[4–10]. The risk is very low in women under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases[11]. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives. (See Table II)

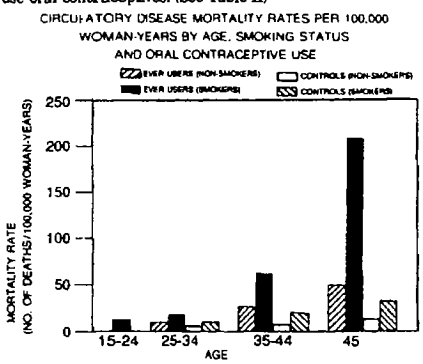


TABLE II. (Adapted from P.M. Layde and V. Beral, ref. #12.)

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.[13] In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism[14–18]. Oral contraceptives have been shown to increase blood pressure among users (see section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease[2,3,19–24]. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization[25]. The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped[2].

A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives[9]. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions[26]. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast feed.

c. Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (> 35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke[27–29]. In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension[30]. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension[30]. The attributable risk is also greater in older women[3].

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease[31–33]. A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents[14–16]. A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive. Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.035 mg or less of estrogen.

e. Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40–49 years old who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups[8]. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small[34]. However, both studies were performed with oral contraceptive formulations containing 0.050 mg or higher of estrogens.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table III). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth.

The observation of an increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's[35]. Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over. The committee concluded that although cardiovascular disease risk may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.

Of course, older women, as all women who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and individual patient needs.

[See Table III at top of next page.]

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. While there are conflicting reports most studies suggest that the use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk appears to be related to duration of use[36–43,79–89].

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women[45–48]. However, there continues to be controversy about the extent to

TABLE I: LOWEST EXPECTED AND TYPICAL FAILURE RATES DURING THE FIRST YEAR OF CONTINUOUS USE OF A METHOD
% of Women Experiencing an Accidental Pregnancy in the First Year of Continuous Use

Method	Lowest Expected*	Typical**
(No Contraceptive)	(85)	(85)
Oral Contraceptives		3
combined	0.1	N/A***
progestin only	0.5	N/A***
Diaphragm with spermicidal cream or jelly	6	18
Spermicides alone (foam, creams, gels, jellies, vaginal suppositories, and vaginal film)	6	21
Vaginal Sponge		
nulliparous	9	18
parous	20	36
Implant	0.09	0.09
Injection: depot medroxyprogesterone acetate	0.3	0.3
IUD		
progesterone	1.5	2.0
copper T 380A	0.6	0.8
Condom without spermicides		
female	5	21
male	3	12
Cervical Cap with spermicidal cream or jelly		
nulliparous	9	18
parous	26	36
Periodic abstinence (all methods)	1–9	20
Female sterilization	0.4	0.4
Male sterilization	0.10	0.15

Adapted from RA Hatcher et al, Table 5–2, (1994) ref. #1.

* The authors' best guess of the percentage of women expected to experience an accidental pregnancy among couples who initiate a method (not necessarily for the first time) and who use it consistently and correctly during the first year if they do not stop for any other reason.

** This term represents "typical" couples who initiate use of a method (not necessarily for the first time), who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

*** N/A—Data not available.

which such findings may be due to differences in sexual behavior and other factors.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher dose[49]. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage[50,51].

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma[52–54] in long-term (> 8 years) oral contraceptive users. However, these cancers are rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy[55–57]. The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned[55,56,58,59], when oral contraceptives are taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens[60,61]. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal[62–64]. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users[17]. This effect has been shown to be directly related to estrogen dose[65]. In general, progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents[17,66]. In the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose[67]. Because of these demonstrated effects, prediabetic and diabetic women should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1.a. and 1.d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives[68] and this increase is more likely in older oral contraceptive users[69] and with extended duration of use[61]. Data from the Royal College of General Practitioners[12] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.

Women with a history of hypertension or hypertension-related diseases, or renal disease[70] should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives[69], and there is no difference in the occurrence of hypertension among former and never users[68,70,71].

10. HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

TABLE III—ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15–19	20–24	25–29	30–34	35–39	40–44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth-related
** Deaths are method-related

Adapted from H.W. Ory, ref. #35.

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

12. ECTOPIC PREGNANCY

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS

1. PHYSICAL EXAMINATION AND FOLLOW UP

It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

3. LIVER FUNCTION

If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

5. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

6. CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

7. DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, carbamazepine and possibly with griseofulvin, ampicillin and tetracyclines[72].

8. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

c. Other binding proteins may be elevated in serum.

d. Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids however, free or biologically active levels either decrease or remain unchanged.

e. High-density lipoprotein (HDL-C) and triglycerides may be increased, while low-density lipoprotein cholesterol (LDL-C) and total cholesterol (Total-C) may be decreased or unchanged.

f. Glucose tolerance may be decreased.

g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

9. CARCINOGENESIS

See WARNINGS section.

10. PREGNANCY

Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS sections.

11. NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

12. SEXUALLY TRANSMITTED DISEASES

Patients should be counseled that this product does not provide against HIV infection (AIDS) and other sexually transmitted diseases.

INFORMATION FOR THE PATIENT

See Patient Labeling Printed Below

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS section).

- Thrombophlebitis and venous thrombosis with or without embolism
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gall bladder disease
- Hepatic adenomas or benign liver tumors

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:

- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema
- Melasma which may persist
- Breast changes: tenderness, enlargement, secretion
- Change in weight (increase or decrease)
- Change in cervical erosion and secretion
- Diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine
- Rash (allergic)
- Mental depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

Continued on next page

Ortho—Cont.

- Pre-menstrual syndrome
- Cataracts
- Changes in appetite
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis
- Porphyria
- Impaired renal function
- Hemolytic uremic syndrome
- Acne
- Changes in libido
- Colitis
- Budd-Chiari Syndrome

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol[73–78].

Effects on menses:

- increased menstrual cycle regularity
- decreased blood loss and decreased incidence of iron deficiency anemia
- decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:

- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancies

Effects from long-term use:

- decreased incidence of fibroadenomas and fibrocystic disease of the breast
- decreased incidence of acute pelvic inflammatory disease
- decreased incidence of endometrial cancer
- decreased incidence of ovarian cancer

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, ORTHO-CEPT must be taken exactly as directed and at intervals not exceeding 24 hours. ORTHO-CEPT is available in the DIALPAK® Tablet Dispenser which is preset for a Sunday Start. Day 1 start is also provided.

21-Day Regimen (Day 1 Start)

The dosage of ORTHO-CEPT 21 for the initial cycle of therapy is one tablet administered daily from the 1st day through the 21st day of the menstrual cycle, counting the first day of menstrual flow as "Day 1". For subsequent cycles, no tablets are taken for 7 days, then a new course is started of one tablet a day for 21 days. The dosage regimen then continues with 7 days of no medication, followed by 21 days of medication, instituting a three-weeks-on, one-week-off dosage regimen.

The use of ORTHO-CEPT 21 for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS for "Nursing Mothers".) If the patient starts on ORTHO-CEPT postpartum, and has not yet had a period, she should be instructed to use another method of contraception until an orange tablet has been taken daily for 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered. If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

21-Day Regimen (Sunday Start)

When taking ORTHO-CEPT 21, the first orange tablet should be taken on the first Sunday after menstruation begins. If period begins on Sunday, the first orange tablet is taken on that day. If switching directly from another oral contraceptive, the first orange tablet should be taken on the first Sunday after the last ACTIVE tablet of the previous product. One orange tablet is taken daily for 21 days. For subsequent cycles, no tablets are taken for seven days, then a new course is started of one tablet a day for 21 days instituting a 3-weeks-on, one-week-off dosage regimen. When initiating a Sunday start regimen, another method of contraception should be used until after the first 7 consecutive days of administration.

The use of ORTHO-CEPT 21 for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS for "Nursing Mothers".) If the patient starts on ORTHO-CEPT postpartum, and has not yet had a period, she should be instructed to use another method of contraception until an orange tablet has been taken daily for 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered. If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

28-Day Regimen (Day 1 Start)

The dosage of ORTHO-CEPT 28 for the initial cycle of therapy is one tablet administered daily from the 1st day through 21st day of the menstrual cycle, counting the first day of menstrual flow as "Day 1". Tablets are taken without interruption as follows: One orange tablet daily for 21 days, then one green tablet daily for 7 days. After 28 tablets have been taken, a new course is started and an orange tablet is taken the next day.

The use of ORTHO-CEPT 28 for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS for "Nursing Mothers".) If the patient starts on ORTHO-CEPT postpartum, and has not yet had a period, she should be instructed to use another method of contraception until an orange tablet has been taken daily for 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered. If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

28-Day Regimen (Sunday Start)

When taking ORTHO-CEPT 28, the first orange tablet should be taken on the first Sunday after menstruation begins. If period begins on Sunday, the first orange tablet is taken on that day. If switching directly from another oral contraceptive, the first orange tablet should be taken on the first Sunday after the last ACTIVE tablet of the previous product. Tablets are taken without interruption as follows: One orange tablet daily for 21 days, then one green tablet daily for 7 days. After 28 tablets have been taken, a new course is started and an orange tablet is taken the next day (Sunday). When initiating a Sunday start regimen, another method of contraception should be used until after the first 7 consecutive days of administration.

The use of ORTHO-CEPT 28 for contraception may be initiated 4 weeks postpartum. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS for "Nursing Mothers".) If the patient starts on ORTHO-CEPT postpartum, and has not yet had a period, she should be instructed to use another method of contraception until an orange tablet has been taken daily for 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered. If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses three (3) or more tablets in a row, the patient should continue taking one tablet every day until Sunday. On Sunday the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

ALL ORAL CONTRACEPTIVES

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Use of oral contraceptives in the event of a missed menstrual period:

1. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptive use should be discontinued until pregnancy is ruled out.
2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use.

HOW SUPPLIED

ORTHO-CEPT® 21 Tablets are available in a DIALPAK® Tablet Dispenser (NDC 0062-1796-15) containing 21 orange tablets (0.15 mg desogestrel and 0.03 mg ethinyl estradiol) which are unscored with "ORTHO" on one side and "D 150" on the opposite side.

ORTHO-CEPT 21 is available for clinic usage in a VERIDATE® Tablet Dispenser (unfilled) and VERIDATE Refills (NDC 0062-1795-20).

ORTHO-CEPT 28 Tablets are available in a DIALPAK Tablet Dispenser (NDC 0062-1796-15) containing 28 tablets, as follows: 21 orange tablets as described under ORTHO-CEPT 21, and 7 green tablets containing inert ingredients.

ORTHO-CEPT 28 is available for clinic usage in a VERIDATE Tablet Dispenser (unfilled) and VERIDATE Refills (NDC 0062-1796-20).

STORAGE: Store before 86° F (30° C).

CAUTION

Federal law prohibits dispensing without prescription.

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BRIEF SUMMARY PATIENT PACKAGE INSERT

Oral contraceptives, also known as "birth control pills" or "the pill", are taken to prevent pregnancy, and when taken correctly, have a failure rate of about 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women, oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be life-threatening or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice or malignant or benign liver tumors

Although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy, non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, headache, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting, may subside within the first three months of use.

Continued on next page

Ortho—Cont.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:
1. Blood clots in the legs (thrombophlebitis) or lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack or angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes, and subsequent serious medical consequences.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.
The symptoms associated with these serious side effects are discussed in the detailed patient labeling given to you with your supply of pills. Notify your doctor or clinic if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics may decrease oral contraceptive effectiveness.
There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer. Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.
Taking the pill provides some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, few pelvic infections, and fewer cancers of the ovary and the lining of the uterus.
Be sure to discuss any medical condition you may have with your doctor or clinic. Your doctor or clinic will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health care provider believes that it is good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information labeling gives you further information which you should read and discuss with your doctor or clinic.
This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DETAILED PATIENT LABELING

PLEASE NOTE: This labeling is revised from time to time as important new medical information becomes available. Therefore, please review this labeling carefully.
The following oral contraceptive products contain a combination of a progestogen and estrogen, the two kinds of female hormones:

ORTHO-CEPT® ☐ 21 Day Regimen
ORTHO-CEPT® ☐ 28 Day Regimen
Each orange tablet contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol. Each green tablet in the ORTHO-CEPT 28 day regimen contains inert ingredients.

INTRODUCTION

Any woman who considers using oral contraceptives (the birth control pill or the pill) should understand the benefits and risks of using this form of birth control. This patient labeling will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this labeling is not a replacement for a careful discussion between you and your doctor or clinic. You should discuss the information provided in this labeling with him or her, both when you first start taking the pill and during your revisits. You should also follow your doctor's or clinic's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth control pills" or "the pill" are used to prevent pregnancy and are more effective than other non-surgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use) when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.
In comparison, typical failure rates for other non-surgical methods of birth control during the first year of use are as follows:
Implant: <1%
Injection: <1%
IUD: 1 to 2%
Diaphragm with spermicides: 18%
Spermicides alone: 21%
Vaginal sponge: 18 to 36%
Cervical Cap: 18 to 36%
Condom alone (male): 12%
Condom alone (female): 21%
Periodic abstinence: 20%
No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives are strongly advised not to smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have any of the following conditions:
- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

Tell your doctor or clinic if you have ever had any of these conditions. Your doctor or clinic can recommend another method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your doctor or clinic if you have or have had:
- Breast nodules, fibrocystic disease of the breast, an abnormal breast x-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Migraine or other headaches or epilepsy
- Mental depression
- Gallbladder, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their doctor or clinic if they choose to use oral contraceptives.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	15–19	20–24	25–29	30–34	35–39	40–44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth-related
** Deaths are method-related

Also, be sure to inform your doctor or clinic if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risk of developing blood clots
Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.
If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor or clinic about stopping oral contraceptives three to four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for at least four weeks after delivery if you are not breast feeding or four weeks after a second trimester abortion. If you are breast feeding, you should wait until you have weaned your child before using the pill. (See also the section on Breast Feeding in General Precautions.)
The risk of circulatory disease in oral contraceptive users may be higher in users of high dose pills and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.
2. Heart attacks and strokes
Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.
Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.
3. Gallbladder disease
Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.
4. Liver tumors
In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in two studies, in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are rare.
5. Cancer of the reproductive organs and breasts
There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer.
Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table. [See table at left.]
In the above table, the risk of death from any birth control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7–26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death is always lower than that associated with preg-

nancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of low-dose oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor or clinic immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or clinic to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark colored urine, or light colored bowel movements (indicating possible liver problems)

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. Vaginal bleeding

Irregular vaginal bleeding or spotting may occur while you are taking the pills. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle or lasts for more than a few days, talk to your doctor or clinic.

2. Contact lenses

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or clinic.

3. Fluid retention

Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or clinic.

4. Melasma

A spotty darkening of the skin is possible, particularly of the face, which may persist.

5. Other side effects

Other side effects may include nausea and vomiting, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.

If any of these side effects bother you, call your doctor or clinic.

GENERAL PRECAUTIONS

1. Missed periods and use of oral contraceptives before or during early pregnancy

There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your doctor or clinic before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, you may be pregnant. If you missed two consecutive menstrual periods, you may be pregnant. Check with your doctor or clinic immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

There is no conclusive evidence that oral contraceptive use is associated with an increase in birth defects, when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these findings have not been seen in more recent studies. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor or clinic. You should check with your doctor or clinic about risks to your unborn child of any medication taken during pregnancy.

2. While breast feeding

If you are breast feeding, consult your doctor or clinic before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, oral contraceptives may decrease the amount and quality of your milk. If possible, do not use oral contraceptives while breast feeding. You should use another method of contraception since breast feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast feed for longer periods of time. You should consider starting oral contraceptives only after you have weaned your child completely.

3. Laboratory tests

If you are scheduled for any laboratory tests, tell your doctor or clinic you are taking birth control pills. Certain blood tests may be affected by birth control pills.

4. Drug interactions

Certain drugs may interact with birth control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital), anticonvulsants such as carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand), and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. Sexually transmitted diseases

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1–3 PACKS OF PILLS. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:
The 21-pill pack has 21 "active" orange pills (with hormones) to take for 3 weeks, followed by 1 week without pills.
The 28-pill pack has 21 "active" orange pills (with hormones) to take for 3 weeks, followed by 1 week of reminder green pills (without hormones).
3. ALSO FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills.

CHECK PICTURE OF PILL PACK AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE IN THE BRIEF SUMMARY PATIENT PACKAGE INSERT.

4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam, or sponge) to use as a back-up method in case you miss pills.
AN EXTRA, FULL PILL PACK

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. ORTHO-CEPT is available in the DIALPAK® Tablet Dispenser which is preset for a Sunday Start. Day 1 start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START:

1. Take the first "active" orange pill of the first pack during the first 24 hours of your period.
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:

1. Take the first "active" orange pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

WHAT TO DO DURING THE MONTH

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.

Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:

21 pills: Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.

28 pills: Start the next pack on the day after your last "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** orange "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** orange "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 2** orange "active" pills in a row in **THE 3RD WEEK:**

If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.

If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.

2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** orange "active" pills in a row (during the first 3 weeks).

If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.

If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday. On Sunday THROW OUT the rest of the pack and start a new pack of pills that same day.

2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

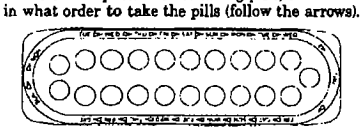
Continued on next page

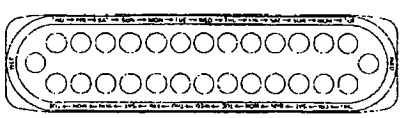
IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:
1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS.
If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.
NORDETTE®- 21, OVRAL®, LO/OVRAL®, NORDETTE®-28, OVRAL®-28, AND LO/OVRAL®-28

***BEFORE* YOU START TAKING YOUR PILLS**

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:
The *21-pill pack* has 21 "active" white or light-orange pills (with hormones) to take for 3 weeks, followed by 1 week without pills.
The *28-pill pack* has 21 "active" white or light-orange pills (with hormones) to take for 3 weeks, followed by 1 week of reminder pink pills (without hormones).
3. ALSO FIND:
1) where on the pack to start taking pills, and
2) in what order to take the pills (follow the arrows).





4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foams or sponge) to use as a back-up in case you miss pills.
AN EXTRA, FULL PILL PACK.

WHEN TO START THE *FIRST* PACK OF PILLS

For the 21-day pill pack you have two choices of which day to start taking your first pack of pills. (See **DAY 1 START** or **SUNDAY START** directions below.) Decide with your doctor or clinic which is the best day for you. The 28-day pill pack accommodates a **SUNDAY START** only. For either pill pack pick a time of day which will be easy to remember.
DAY 1 START:
These instructions are for the 21-day pill pack only. The 28-day pill pack does not accommodate a **DAY 1 START** dosage regimen.
1. Take the first "active" white or light-orange pill of the first pack during the *first 24 hours of your period.*
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.
SUNDAY START:
These instructions are for either the 21-day or the 28-day pill pack.
1. Take the first "active" white or light-orange pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. *Use another method of birth control* as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

WHAT TO DO DURING THE MONTH

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.
2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:
21 pills: Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.
28 pills: Start the next pack on the day after your last "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS** 1 white or light-orange "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.
If you **MISS 2** white or light-orange "active"pills in a row in **WEEK 1** or **WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.
If you **MISS 2** white or light-orange "active" pills in a row in **THE 3rd WEEK**:
The ***Day 1 Starter*** instructions are for the 21-day pill pack only. The 28-day pill pack does not accommodate a **DAY 1 START** dosage regimen. The ***Sunday Starter*** instructions are for either the 21-day or 28-day pill pack.
1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.
If you **MISS 3 OR MORE** white or light-orange "active" pills in a row (during the first 3 weeks):
The ***Day 1 Starter*** instructions are for the 21-day pill pack only. The 28-day pill pack does not accommodate a **DAY 1 START** dosage regimen. The ***Sunday Starter*** instructions are for either the 21-day or 28-day pill pack.
1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:
If you forget any of the 7 pink "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method if you start your next pack on time.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:
Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE PILL EACH DAY until you can reach your doctor or clinic.
OVRETTE®
Ovrette is administered on a continuous daily dosage schedule, one tablet each day, every day of the year. Take the first tablet on the first day of your menstrual period. Tablets should be taken at the same time every day, without interruption, whether bleeding occurs or not. If bleeding is prolonged (more than 8 days) or unusually heavy, you should contact your doctor.
Forgotten pills
The risk of pregnancy increases with each tablet missed. Therefore, it is very important that you take one tablet daily as directed. If you miss one tablet, take it as soon as you remember and also take your next tablet at the regular time. If you miss two tablets, take one of the missed tablets as soon as you remember, as well as your regular tablet for that day at the proper time. Furthermore, you should use another method of birth control in addition to taking Ovrette until you have taken fourteen days (2 weeks) of medication.
If more than two tablets have been missed, Ovrette should be discontinued immediately and another method of birth control used until the start of your next menstrual period. Then you may resume taking Ovrette.

Pregnancy due to pill failure
The incidence of pill failure resulting in pregnancy is approximately less than 1.0% if taken every day as directed, but more typical failure rates are less than 3.0%. If failure does occur, the risk to the fetus is minimal.
RISKS TO THE FETUS
If you do become pregnant while using oral contraceptives, the risk to the fetus is small, on the order of no more than one per thousand. You should, however, discuss the risks to the developing child with your doctor.
Pregnancy after stopping the pill
There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.
There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.
Overdosage
Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health-care provider or pharmacist.
Other information
Your health-care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health-care provider believes that it is appropriate to postpone it. You should be reexamined at least once a year. Be sure to inform your health-care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health-care provider, because this is a time to determine if there are early signs of side effects of oral-contraceptive use.
Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth-control pills.
HEALTH BENEFITS FROM ORAL CONTRACEPTIVES
In addition to preventing pregnancy, use of oral contraceptives may provide certain benefits. They are:
- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter, and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently
- Ovarian cysts may occur less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Noncancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral-contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your doctor or pharmacist. They have a more technical leaflet called the Professional Labeling which you may wish to read.

Shown in Product Identification Guide, page 340

LO/OVRAL®-28 ℞
[lōh-oh 'vral-28]
Tablets
(norgestrel and ethinyl estradiol tablets)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Continued on next page

Wyeth-Ayerst Laboratories—Cont.

DESCRIPTION

21 white LO/OVRAL tablets, each containing 0.3 mg of norgestrel (*dl*-13-beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), a totally synthetic progestogen, and 0.03 mg of ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol), and 7 pink inert tablets. The inactive ingredients present are cellulose, D&C Red 30, lactose, magnesium stearate, and polacrilin potassium.

CLINICAL PHARMACOLOGY

See LO/OVRAL®.

INDICATIONS AND USAGE

See LO/OVRAL.

CONTRAINDICATIONS

See LO/OVRAL.

WARNINGS

See LO/OVRAL.

PRECAUTIONS

See LO/OVRAL.

Drug Interactions: See LO/OVRAL.
Carcinogenesis: See LO/OVRAL.
Pregnancy: See LO/OVRAL.
Nursing Mothers: See LO/OVRAL.
Information for the Patient: See LO/OVRAL.

ADVERSE REACTIONS

See LO/OVRAL.

OVERDOSAGE

See LO/OVRAL.

NONCONTRACEPTIVE HEALTH BENEFITS

See LO/OVRAL.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, LO/OVRAL-28 must be taken exactly as directed and at intervals not exceeding 24 hours.

The dosage of LO/OVRAL-28 is one white tablet daily for 21 consecutive days followed by one pink inert tablet daily for 7 consecutive days according to prescribed schedule. It is recommended that tablets be taken at the same time each day, preferably after the evening meal or at bedtime.

During the first cycle of medication, the patient is instructed to begin taking LO/OVRAL-28 on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first tablet (white) is taken that day. One white tablet should be taken daily for 21 consecutive days followed by one pink inert tablet daily for 7 consecutive days. Withdrawal bleeding should usually occur within three days following discontinuation of white tablets. During the first cycle, contraceptive reliance should not be placed on LO/OVRAL-28 until a white tablet has been taken daily for 7 consecutive days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient begins her next and all subsequent 28-day courses of tablets on the same day of the week (Sunday) on which she began her first course, following the same schedule: 21 days on white tablets—7 days on pink inert tablets. If in any cycle the patient starts tablets later than the proper day, she should protect herself by using another method of birth control until she has taken a white tablet daily for 7 consecutive days.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician. Although the occurrence of pregnancy is highly unlikely if LO/OVRAL-28 is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

For additional patient instructions regarding missed pills, see the "WHAT TO DO IF YOU MISS PILLS" section in the **DETAILED PATIENT LABELING** for LO/OVRAL.

Any time the patient misses two or more white tablets, she should also use another method of contraception until she has taken a white tablet daily for seven consecutive days. If the patient misses one or more pink tablets, she is still protected against pregnancy provided she begins taking white tablets again on the proper day.

If breakthrough bleeding occurs following missed white tablets, it will usually be transient and of no consequence. While there is little likelihood of ovulation occurring if only one or two white tablets are missed, the possibility of ovulation increases with each successive day that scheduled white tablets are missed.

In the nonlactating mother, LO/OVRAL-28 may be initiated postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered (see "Contraindications", "Warnings", and "Precautions" concerning thromboembolic disease). It is to be noted that early resumption of ovulation may occur if Parlodel® (bromocriptine mesylate) has been used for the prevention of lactation.

HOW SUPPLIED

LO/OVRAL®-28 Tablets (0.3 mg norgestrel and 0.03 mg ethinyl estradiol) are available in packages of 6 PILPAK® dispensers, each containing 28 tablets as follows:
21 active tablets, NDC 0008-0078, white, round tablet marked "WYETH" and "78".
7 inert tablets, NDC 0008-0486, pink, round tablet marked "WYETH" and "486".

ALSO AVAILABLE:
LO/OVRAL®-28 Tablets (0.3 mg norgestrel and 0.03 mg ethinyl estradiol) are available in packages of 12 PILPAK® dispensers for clinic use only, each containing 28 tablets as follows:
21 active tablets, NDC 0008-0078, white, round tablet marked "WYETH" and "78".
7 inert tablets, NDC 0008-0486, pink, round tablet marked "WYETH" and "486".

References available upon request.

Brief Summary Patient Package Insert: See LO/OVRAL.
DETAILED PATIENT LABELING: See LO/OVRAL.

HOW TO TAKE THE PILL

For Lo/Ovral-28 PILPAK® Dispenser, See LO/OVRAL.
For Lo/Ovral-28 Clinic Pilpak®, See below.

HOW TO TAKE THE PILL

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.

3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1–3 PACKS OF PILLS.
If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.

4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.

6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

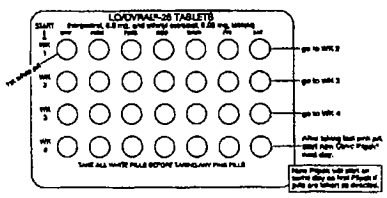
NORDETTE®-21, OVRAL®, LO/OVRAL®, NORDETTE®-28, OVRAL®-28, AND LO/OVRAL®-28

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.

2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:
The *21-pill pack* has 21 "active" white or light-orange pills (with hormones) to take for 3 weeks, followed by 1 week without pills.
The *28-pill pack* has 21 "active" white or light-orange pills (with hormones) to take for 3 weeks, followed by 1 week of reminder pink pills (without hormones).

3. ALSO FIND:
1) where on the pack to start taking pills,
2) in what order to take the pills (follow the arrows), and
3) the week numbers as shown in the picture below.



4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up in case you miss pills.
AN EXTRA, FULL PILL PACK.

WHEN TO START THE *FIRST* PACK OF PILLS:

For the 21-day pill pack you have two choices of which day to start taking your first pack of pills. (See **DAY 1 START** or **SUNDAY START** directions below.) Decide with your doctor or clinic which is the best day for you. The 28-day pill pack accommodates a **SUNDAY START** only. For either pill pack pick a time of day which will be easy to remember.

DAY 1 START:
These instructions are for the 21-day pill pack only. The 28-day pill pack does not accommodate a **DAY 1 START** dosage regimen.
1. Take the first "active" white or light-orange pill of the first pack during the *first 24 hours of your period.*
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:
These instructions are for either the 21-day or the 28-day pill pack.
1. Take the first "active" white or light-orange pill of the first pack on the *Sunday after your period starts,* even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. *Use another method of birth control* as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

WHAT TO DO DURING THE MONTH:

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:
21 pills: Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.
28 pills: Start the next pack on the day after your last "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** white or light-orange "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** white or light-orange "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the 7 *days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 2** white or light-orange "active" pills in a row in **THE 3rd WEEK:**
The **Day 1 Starter** instructions are for the 21-day pill pack only. The 28-day pill pack does not accommodate a **DAY 1 START** dosage regimen. The **Sunday Starter** instructions are for either the 21-day or 28-day pill pack.
1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.

2. You may not have your period this month but this is expected.
However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 *days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.
If you **MISS 3 OR MORE** white or light-orange "active" pills in a row (during the first 3 weeks):
The **Day 1 Starter** instructions are for the 21-day pill pack only. The 28-day pill pack does not accommodate a **DAY 1 START** dosage regimen. The **Sunday Starter** instructions are for either the 21-day or 28-day pill pack.
1. ***If you are a Day 1 Starter:***
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday.
On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected.
However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 *days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:
If your forget any of the 7 pink "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method if you start your next pack on time.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:
Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE PILL EACH DAY until you can reach your doctor or clinic.

OVRETTE®

Ovrette is administered on a continuous daily dosage schedule, one tablet each day, every day of the year. Take the first tablet on the first day of your menstrual period. Tablets should be taken at the same time every day without interruption, whether bleeding occurs or not. If bleeding is prolonged (more than 8 days) or unusually heavy, you should contact your doctor.

Forgotten pills

The risk of pregnancy increases with each tablet missed. Therefore, it is very important that you take one tablet daily as directed. If you miss one tablet, take it as soon as you remember and also take your next tablet at the regular time. If you miss two tablets, take one of the missed tablets as soon as you remember, as well as your regular tablet for that day at the proper time. Furthermore, you should use another method of birth control in addition to taking Ovrette until you have taken fourteen days (2 weeks) of medication.
If more than two tablets have been missed, Ovrette should be discontinued immediately and another method of birth control used until the start of your next menstrual period. Then you may resume taking Ovrette.

Pregnancy due to pill failure

The incidence of pill failure resulting in pregnancy is approximately less than 1.0% if taken every day as directed, but more typical failure rates are less than 3.0%. If failure does occur, the risk to the fetus is minimal.

RISKS TO THE FETUS

If you do become pregnant while using oral contraceptives, the risk to the fetus is small, on the order of no more than one per thousand. You should, however, discuss the risks to the developing child with your doctor.

Pregnancy after stopping the pill

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.
There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

Overdosage

Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health-care provider or pharmacist.

Other information

Your health-care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health-care provider believes that it is appropriate to postpone it. You should be reexamined at least once a year. Be sure to inform your health-care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health-care provider, because this is a time to determine if there are early signs of side effects of oral-contraceptive use.
Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth-control pills.
HEALTH BENEFITS FROM ORAL CONTRACEPTIVES:
See Lo/OVRAL.

Shown in Product Identification Guide, page 340

MAZANOR®

[*maz'a-nor*]
(mazindol)

DESCRIPTION

Mazanor (mazindol) is an imidazoisoindole anorectic agent. It is chemically designated as 5-p-chloro-phenyl-5-hydroxy-2,3-dihydro-5H-imidazo (2,1-a) isoindole, a tautomeric form of 2-[2'-(p-chlorobenzoyl) phenyl]-2-imidazoline. Mazanor tablets contain 1 mg mazindol. The inactive ingredients present are calcium sulfate, cellulose, lactose, magnesium stearate, povidone, and talc.

HOW SUPPLIED

Mazanor® (mazindol) Tablets are available in the following dosage strength in bottles of 30 tablets:
1 mg, NDC 0008-0071-03, white, round, scored tablet marked "WYETH" and "71".
Keep tightly closed.
Store below 25° C (77° F).
Dispense in tight container.
For prescribing information, write to Professional Service, Wyeth-Ayerst Laboratories, P.O. Box 8299, Philadelphia, PA 19101, or contact your local Wyeth-Ayerst representative.

MEPERGAN®

[*mep'er-gan*]
(meperidine HCl and promethazine HCl) Injection

DESCRIPTION

This product is available in concentration providing 25 mg each of meperidine hydrochloride and promethazine hydrochloride per mL with 0.1 mg edetate disodium, 0.04 mg calcium chloride, and not more than 0.75 mg sodium formaldehyde sulfoxylate, 0.25 mg sodium metabisulfite, and 5 mg phenol with sodium acetate buffer.

ACTIONS

Meperidine hydrochloride is a narcotic analgesic with multiple actions qualitatively similar to those of morphine. Phenergan®, promethazine HCl, is a phenothiazine derivative that has several different pharmacologic properties including antihistaminic, sedative, and antiemetic actions.

INDICATIONS

As a preanesthetic medication when analgesia and sedation are indicated. As an adjunct to local and general anesthesia.

CONTRAINDICATIONS

Hypersensitivity to meperidine or promethazine.
Under no circumstances should Mepergan be given by intra-arterial injection, due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see "Warnings").
Mepergan should not be given by the subcutaneous route; evidence of chemical irritation has been noted, and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.
Meperidine is contraindicated in patients who are receiving monoamine oxidase inhibitors (MAOI) or those who have received such agents within 14 days. Therapeutic doses of meperidine have inconsistently precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received such agents within 14 days. The mechanism of these reactions is unclear. Some have been characterized by coma, severe respiratory depression, cyanosis, and hypotension and have resembled the syndrome of acute narcotic overdose. In other reactions the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension. Although it is not known that other narcotics are free of the risk of such reactions, virtually all of the reported reactions have occurred with meperidine. If a narcotic is needed in such patients, a sensitivity test should be performed in which repeated, small, incremental doses of morphine are administered over the course of several hours while the patient's condition and vital signs are under careful observation.
(Intravenous hydrocortisone or prednisolone have been used to treat severe reactions, with the addition of intravenous chlorpromazine in those cases exhibiting hypertension and hyperpyrexia. The usefulness and safety of narcotic antagonists in the treatment of these reactions is unknown.)

WARNINGS

Mepergan Injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.
Tolerance and Addiction Liability
Warning—may be habit-forming
DRUG DEPENDENCE
Meperidine can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of meperidine, and it should be prescribed and administered with the same degree of caution appropriate to the use of morphine. Like other narcotics, meperidine is subject to the provisions of the Federal narcotic laws.
INTERACTION WITH OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS
Meperidine should be used with great caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.
The sedative action of promethazine hydrochloride is additive to the sedative effects of central nervous system depressants; therefore, agents such as alcohol, barbiturates, and narcotic analgesics should either be eliminated or given in reduced dosage in the presence of promethazine hydrochloride. When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half and the dose of analgesic depressants, such as morphine or meperidine, should be reduced by one-quarter to one-half.
HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE
The respiratory-depressant effects of meperidine and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, meperidine must be used with extreme caution and only if its use is deemed essential.
INADVERTENT INTRA-ARTERIAL INJECTION
Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection of Mepergan. Reports compatible with inadvertent intra-arterial injection suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation is likely under such circumstances. Intravenous injection was intended in all the cases reported, but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of this condition after it occurs, although sympathetic block and heparinization are commonly employed during the acute management because of the results of animal experiments with other known arteriolar irritants. Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with promethazine. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.
INTRAVENOUS USE
If necessary, meperidine may be given intravenously, but the injection should be given very slowly, preferably in the form of a diluted solution. Rapid intravenous injection of narcotic analgesics, including meperidine, increases the incidence of adverse reactions; severe respiratory depression, apnea, hypotension, peripheral circulatory collapse, and cardiac arrest have occurred. Meperidine should not be administered intravenously unless a narcotic antagonist and the facilities for assisted or controlled respiration are immediately available. When meperidine is given parenterally, especially intravenously, the patient should be lying down.
When used intravenously, Mepergan should be given at a rate not to exceed 1 mL (25 mg of each component) per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain dur-

Continued on next page

Bristol-Myers Squibb Co.—Cont.

OVERDOSAGE

Oral doses of fosinopril at 2600 mg/kg in rats were associated with significant lethality. Human overdoses of fosinopril have not been reported, but the most common manifestation of human fosinopril overdosage is likely to be hypotension. Laboratory determinations of serum levels of fosinoprilat and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of fosinopril overdose. No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of fosinopril and its metabolites. Fosinoprilat is poorly removed from the body by both hemodialysis and peritoneal dialysis.

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of fosinopril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of fosinopril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat fosinopril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

Hypertension

The recommended initial dose of MONOPRIL (Fosinopril Sodium) is 10 mg once a day, both as monotherapy and when the drug is added to a diuretic. Dosage should then be adjusted according to blood pressure response at peak (2–6 hours) and trough (about 24 hours after dosing) blood levels. The usual dosage range needed to maintain a response at trough is 20–40 mg but some patients appear to have a further response to 80 mg. In some patients treated with once daily dosing, the antihypertensive effect may diminish toward the end of the dosing interval. If trough response is inadequate, dividing the daily dose should be considered. If blood pressure is not adequately controlled with MONOPRIL alone, a diuretic may be added.

Concomitant administration of MONOPRIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium (see PRECAUTIONS).

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of MONOPRIL. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with MONOPRIL (see WARNINGS). Then, if blood pressure is not controlled with MONOPRIL alone, diuretic therapy should be resumed. If diuretic therapy cannot be discontinued, an initial dose of 10 mg of MONOPRIL should be used with careful medical supervision for several hours and until blood pressure has stabilized. (See WARNINGS; PRECAUTIONS: Information for Patients and Drug Interactions.)

Since concomitant administration of MONOPRIL (Fosinopril Sodium) with potassium supplements, or potassium-containing salt substitutes or potassium-sparing diuretics may lead to increases in serum potassium, they should be used with caution. (See PRECAUTIONS).

Heart Failure

Digitalis is not required for MONOPRIL to manifest improvements in exercise tolerance and symptoms. Most placebo-controlled clinical trial experience has been with both digitalis and diuretics present as background therapy.

The usual starting dose of MONOPRIL should be 10 mg once daily. Following the initial dose of MONOPRIL, the patient should be observed under medical supervision for at least two hours for the presence of hypotension or orthostasis and, if present, until blood pressure stabilizes. An initial dose of 5 mg is preferred in heart failure patients with moderate to severe renal failure or those who have been vigorously diuresed.

Dosage should be increased, over a several week period, to a dose that is maximal and tolerated but not exceeding 40 mg once daily. The usual effective dosage range is 20 to 40 mg once daily.

The appearance of hypotension, orthostasis, or azotemia early in dose titration should not preclude further careful dose titration. Consideration should be given to reducing the dose of concomitant diuretic.

For Hypertensive or Heart Failure Patients With Renal Impairment: In patients with impaired renal function, the total body clearance of fosinoprilat is approximately 50% slower than in patients with normal renal function. Since hepatobiliary elimination partially compensates for diminished renal elimination, the total body clearance of fosinoprilat does not differ appreciably with any degree of renal insufficiency (creatinine clearances < 80 mL/min/1.73m^2), including end-stage renal failure (creatinine clearance < 10 mL/min/1.73m^2). This relative constancy of body clearance of active fosinoprilat, resulting from the dual route of elimination, permits use of the usual dose in patients with any degree of renal impairment. (See WARNINGS: Anaphylactoid reactions during membrane exposure and PRECAUTIONS: Hemodialysis.)

HOW SUPPLIED

10 mg tablets: White to off-white, biconvex flat-end diamond shaped, compressed partially scored tablets with unilog number **158** and **MJ** on one side and **m** on the other. They are supplied in bottles of 30 (NDC 0087-0158-22), bottles of 90 (NDC 0087-0158-46) and 1000 (NDC 0087-0158-85). Bottles contain a desiccant canister.

20 mg tablets: White to off-white, oval shaped, compressed tablets with unilog number **609** and **MJ** on one side and **m** on the other. They are supplied in bottles of 30 (NDC 0087-0609-41), bottles of 90 (NDC 0087-0609-42) and 1000 (NDC 0087-0609-85). Bottles contain a desiccant canister.

UNIMATIC® unit-dose packs containing 100 tablets are also available for each potency: **10 mg** (NDC 0087-0158-45) and **20 mg** (NDC 0087-0609-45).

STORAGE

Store between 15°C (59°F) and 30°C (86°F). Avoid prolonged exposure to temperatures above 30°C (86°F). Keep bottles tightly closed (protect from moisture).

(J4-502E)

Revised April 1995

Shown in Product Identification Guide, page 307

OVCON® 35 ℞

OVCON® 50

[ōv'kŏn]

(Norethindrone and Ethinyl Estradiol Tablets, USP)

OVCON 35 (21-day)
NSN 6505-01-084-2667

OVCON 35 (28-day)
NSN 6505-01-153-3851

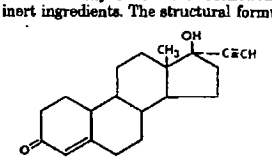
OVCON 50 (28-day)
NSN 6505-01-153-4088

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

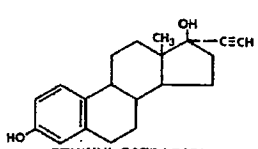
DESCRIPTION

21-Day OVCON 35 provides a regimen for oral contraception derived from 21 tablets composed of norethindrone and ethinyl estradiol. The chemical name for norethindrone is 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one and for ethinyl estradiol the chemical name is 19-nor-17α-pregna-1,3,5 (10)-trien-20-yne-3,17-diol.

28-Day OVCON® 35 and OVCON® 50 (norethindrone and ethinyl estradiol tablets, USP) provide a continuous regimen for oral contraception derived from 21 tablets composed of norethindrone and ethinyl estradiol to be followed by 7 green tablets of inert ingredients. The structural formulas are:



NORETHINDRONE



ETHINYL ESTRADIOL

The active OVCON 35 tablets contain 0.4 mg norethindrone and 0.035 mg ethinyl estradiol. The active OVCON 50 tablets contain 1 mg norethindrone and 0.05 mg ethinyl estradiol. The green tablets contain inert ingredients.

OVCON 35, 21-Day contains the following inactive ingredients: dibasic calcium phosphate, FD&C Yellow No. 6 (aluminum lake), lactose, magnesium stearate, povidone, and sodium starch glycolate.

OVCON 35, 28-Day contains the following inactive ingredients: acacia, dibasic calcium phosphate, D&C Yellow No. 10 (aluminum lake), FD&C Blue No. 1 (aluminum lake), FD&C Yellow No. 6 (aluminum lake), lactose, magnesium stearate, povidone, sodium starch glycolate, starch (corn), and talc.

OVCON 50, 28-Day contains the following inactive ingredients: acacia, dibasic calcium phosphate, D&C Yellow No. 10 (aluminum lake), FD&C Blue No. 1 (aluminum lake), FD&C Yellow No. 6 (aluminum lake), lactose, magnesium stearate, povidone, sodium starch glycolate, starch (corn), and talc.

CLINICAL PHARMACOLOGY

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

INDICATIONS AND USAGE

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.

Oral contraceptives are highly effective. Table 1 lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE 1

LOWEST EXPECTED AND TYPICAL FAILURE RATES DURING THE FIRST YEAR OF CONTINUOUS USE OF A METHOD

% of Women Experiencing an Accidental Pregnancy in the First Year of Continuous Use

Method	Lowest Expected*	Typical**
(No contraception)	(85)	(85)
Oral contraceptives		
combined	0.1	3***
progestin only	0.5	3***
Diaphragm with spermicidal cream or jelly	6	18
Spermicides alone (foam, creams, jellies and vaginal suppositories)	3	21
Vaginal sponge		
nulliparous	6	18
multiparous	9	28
IUD	0.8–2.0	3#
Condom without spermicides	2	12
Periodic abstinence (all methods)	1–9	20
Injectable progestogen	0.3–0.4	0.3–0.4
Implants		
6 capsules	0.04	0.04
2 rods	0.03	0.03
Female sterilization	0.2	0.4
Male sterilization	0.1	0.15

Reproduced with permission of the Population Council from J. Trussell 1 et al: Contraceptive failure in the United States: An update. Studies in Family Planning, 21 (1), January-February 1990.

* The authors' best guess of the percentage of women expected to experience an accidental pregnancy among couples who initiate a method (not necessarily for the first time) and who use it consistently and correctly during the first year if they do not stop for any other reason other than pregnancy.

** This term represents "typical" couples who initiate use of a method (not necessarily for the first time), who experience an accidental pregnancy during the first year if they do not stop use for any other reason other than pregnancy.

*** Combined typical rate for both combined and progestin only.

\# Combined typical rate for both medicated and non-medicated IUD.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebrovascular or coronary artery disease
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity, and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a *ratio* of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population.* For further information, the reader is referred to a text on epidemiological methods.

*Adapted from Stadel BV: Oral contraceptives and cardiovascular disease. *N Engl J Med.* 1981;305:612–618, 672–677; with author's permission.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

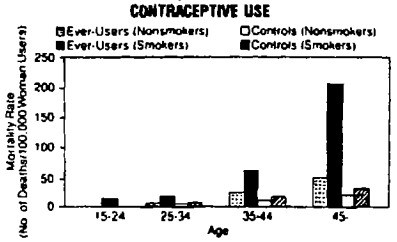
The physician should be alert to the earliest manifestations of thromboembolic thrombotic disorders as discussed below. Should any of these occur or be suspected the drug should be discontinued immediately.

a. Myocardial Infarction

An increased risk of myocardial infarction has been associated with oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older, with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 (Figure 1) among women who use oral contraceptives.

FIGURE 1
CIRCULATORY DISEASE MORTALITY RATES PER 100,000 WOMAN-YEARS BY AGE, SMOKING STATUS AND ORAL CONTRACEPTIVE USE



Layde PM, Beral V: Further analyses of mortality in oral contraceptive users: Royal College of General Practitioners' oral contraceptive study. (Table 5) *Lancet* 1981;1:541–546.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age, and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see section 9 in Warnings). Such increases in risk factors have been associated with an increased risk of heart disease and the risk increases with the number of risk factors present. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

TABLE 2
ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of control and outcome	AGE 15–19	20–24	25–29	30–34	35–39	40–44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives nonsmoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth related
** Deaths are method related

Ory HW: Mortality associated with fertility and fertility control:1983. *Fam Plann Perspect* 1983;15:50–56.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery in women who elect not to breastfeed.

c. Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes); although, in general, the risk is greatest among older (> 35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.05 mg or less of estrogen.

e. Persistence of risk

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40–49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table 2).

[See table above.]

These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risk. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s—but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed (Porter JB, Hunter J, Jick H, et al. Oral contraceptives and nonfatal vascular disease. *Obstet Gynecol* 1985;66:1–4 and Porter JB, Jick H, Walker AM, Mortality among oral contraceptive users. *Obstet Gynecol* 1987;70:29–32), the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risk may be increased with oral contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

3. CARCINOMA OF THE REPRODUCTIVE ORGANS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. The overwhelming evidence in the literature suggests that use of oral contraceptives is not associated with an increase in the risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses. The Cancer and Steroid Hormone (CASH) study also showed no latent effect on the risk of breast cancer for at least a decade following long-term use. A few studies have shown a slightly increased relative risk of developing breast cancer, although the methodology of these studies, which included differences in examination of users and nonusers and differences in age at start of use, has been questioned.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.

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